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Learning objectives	• Discuss multicancer early detection (MCED) testing and the evidence it presents. • Examine two post-hoc analyses of the ASPREE trial around aspirin use and cardiovascular disease, respiratory syncytial virus (RSV) vaccine in older adults and opioid analgesics for low back and neck pain. • Apply medical management in regard to potential harm from oral anticoagulation therapy and the use of shared decision-making in screening and early-stage radiation therapy for breast cancer.

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No commercial support was received for this activity.

MCED for cancer detection

Multicancer early detection (MCED) tests measure circulating tumor DNA (ctDNA). This technology has been studied to guide treatment choices, measure response to therapy and for surveillance of established cancers. However, these tests are now being broadly marketed to both physicians and the general population as tests for early cancer detection. The measure of efficacy with these tests is an improvement in cancer survival. However, there are no randomized controlled studies showing an improvement in cancer survival using MCEDs. One company markets directly to consumers and includes a telemedicine consultation with a physician who orders the test.[1] These tests are being recommended yearly by the manufacturers, on top of the current recommendations for other cancer screening tests. Additionally, there is proposed legislation which would, if approved, create mandatory Medicare coverage for these tests. If these were to be implemented at their current cost of $947 per test for the U.S. population aged 50 and older, the yearly cost would be about $100 billion,[1] or ten times the entire budget for the CDC. This does not include the associated costs of PET-CTs and invasive testing that would be needed to evaluate positive test results.

Although it seems attractive to be able to screen for multiple cancers with a single blood test, let's examine the supporting evidence to date. The prevalence of cancer is very low in healthy asymptomatic people in the general population and, therefore, according to Bayes theorem, these MCED tests will often have positive results in persons without detectable cancer, resulting in a low positive predictive value (PPV), which is the most important statistic to consider. Two "demonstration projects" have documented the findings of MCED testing in prospective cohorts totaling ~16,500 subjects, many of whom had prior cancers, tobacco use or hereditary risk factors, and therefore were not representative of the broad population that would use these tests.[2]

The results can be summarized as follows:

- 3.5% (582) of subjects had a positive test.
- 90% of those (521) were false positives and 10% (61) were true positives.
- In the one study that reported the use of PET-CT for a positive screening test, 50% were normal and 50% found suspicious results. 59% of suspicious results were eventually found negative for cancer after additional evaluations, including some with invasive biopsy.
- Many of the diagnosed cancers were of late stage or recurrent cancers, which were not amenable to cure. Of the 582 positive tests, only 2.4% (14) of the subjects had early-stage solid tumors, which might be amenable to cure. This was 0.0008% of the total screened cohort.
- The most frequently found "true" abnormalities were hematologic (19), which would be expected given that hematologic ctDNA would be most easily detected from blood testing. These represented only 0.001% of the screened cohort.

The harms of the frequent false positive findings cannot be overstated. These harms fall into four categories:

- Psychological harms from patients being told that circulating tumor DNA was found in their blood, but a discrete cancer could not be localized.
- Overdiagnosis and subsequent treatment of indolent cancers that would not have progressed in the patient's lifetime.
- Staggering costs associated with the above evaluations.
- Harms from radiation exposure and invasive diagnostic testing and biopsies. About 1% of screened individuals will subsequently undergo full-body PET-CT, which is typically associated with approximately 36 mGy of radiation, the equivalent of 1,800 chest radiographs. At this rate of PET-CT follow-up, 35 women and 25 men would be estimated to develop cancer for each 1 million persons who underwent these screening blood tests at 40 years of age. Thus, paradoxically, many people who undergo MCED blood testing for cancer screening actually will develop cancer because of this testing.[3]

There is currently only one ongoing RCT looking at MCEDs as a cancer screening tool. It has randomized 14,000 patients in the U.K. to MCED screening versus standard of care. The outcome being measured is the detection of late cancers. Results are anticipated in 2026, although cancer survival, the critical determinant of success in screening, is not being measured in this study. The National Cancer Institute recognizes the need to execute the appropriate trials. They have first planned a trial randomizing 24,000 people into a study to evaluate the feasibility of protocol-defined algorithms for diagnostic testing following abnormal screening test results, in preparation for a larger trial. The larger trial will consist of up to three test groups and a control group receiving standard of care screening alone. It is planned to test all-cancer mortality, over a period of seven to eight years, and include up to 300,000 participants, making it the largest cancer screening trial ever performed. It will likely be a decade before results will be available.

So how best to counsel our patients? Unfortunately, a shared decision-making approach won't work here as the fundamental knowledge necessary to inform the patient is not yet available. However, we do know that there are clear harms associated with MCED testing and to date we do not have any evidence of improved cancer survival. We therefore should not order or encourage our patients to have this testing until data from prospective RCTs becomes available. Additionally, pressure needs to be placed on the FDA to mandate the appropriate evidence of benefit prior to test approval or Medicare coverage.

Two post-hoc analyses of the ASPREE trial: Low-dose aspirin use and anemia in the elderly

New studies do not support the use of aspirin for primary prevention of cardiovascular disease (CVD) in elderly patients, resulting in changes to the USPSTF recommendations for aspirin use.[4] The new guideline recommends shared decision-making in adults ages 40–59 given that the net benefit is small. They recommend against initiating aspirin use for primary prevention of CVD in adults 60 years or older. Although the risk of aspirin-induced major bleeding has been well characterized, the incidence of iron deficiency anemia due to low-dose aspirin use is less well studied. Aspirin in Reducing Events in the Elderly (ASPREE) enrolled over 19,000 community residing individuals without prior stroke or CVD or aspirin contraindications, to a primary prevention study of low-dose aspirin versus placebo to assess both the beneficial and harmful effects of aspirin use in this population.[5] The overall trial did not demonstrate any benefit in survival or reduction in the MACE event rate in the aspirin group. A post-hoc analysis of the risk of iron deficiency anemia with aspirin use formed the basis of this report.[6]

The median duration of follow-up in ASPREE was 4.7 years. Hemoglobin was measured annually. Over the duration of the study, the incidence of iron deficiency anemia was 51 per 1,000 patient-years in the aspirin group compared with 43 per 1,000 patient-years in the placebo group, equating to a 19% higher risk with aspirin use. For the entire study population, serum ferritin declined by 16% in the aspirin group compared with 3% in the placebo group. The incidence of major bleeding during the study was 3% in the aspirin group compared with 2.1% in the placebo group, equating to a 43% higher risk with aspirin use. Because hemoglobin levels declined progressively throughout the study in the aspirin group, long-term aspirin therapy would be expected to have even higher rates of iron deficiency anemia. With the appreciation of the risks of chronic iron deficiency anemia with long term aspirin use, this study adds to the evidence showing harm from aspirin use for primary prevention in the elderly.

Two post-hoc analyses of the ASPREE trial: Harms of low-dose aspirin for primary prevention of stroke in healthy elderly

Low-dose aspirin is no longer routinely promoted for primary prevention of ischemic stroke due to the known associated harms, including complications from increased bleeding risk. A recent secondary analysis of the ASPREE trial[7] examined the risk of hemorrhagic stroke and intracerebral bleeding and found a small but statistically significant increase in risk of these events in people on long-term low-dose aspirin, and no difference in ischemic stroke compared to placebo.[8] The study population included over 19,000 adults older than 64, with the majority age 70 and older, who were free of symptomatic cardiovascular disease and were randomized to take daily 100 mg of enteric-coated aspirin or placebo, with a median follow-up period of 4.7 years. As event rates were low, calculations were done based on events per 1,000 person-years. There were 0.5 fewer incidents of ischemic stroke per 1,000 person-years of follow-up in the aspirin group. The hazard ratio for ischemic stroke was not significant at 0.89 (95% CI, 0.71-1.11). The intracranial hemorrhage incidence rate was 0.7 higher. When looking across all types of intracranial bleeding (e.g., epidural, subdural hematomas, subarachnoid hemorrhage, intracerebral bleeding/stroke), hazard ratios were significantly higher for those treated with aspirin (108 individuals [1.1%]) compared with those receiving placebo (79 individuals [0.8%]; HR, 1.38; 95% CI, 1.03-1.84; P = 0.03).

These results show that while event rates are relatively low, there is a small, but important risk of intracranial bleeding in those taking aspirin. Use of aspirin for primary prevention of stroke for this population should not be used routinely.

RSV vaccine in older adults should employ shared decision-making

Based on existing vaccine safety data and available evidence of efficacy in decreasing morbidity from respiratory syncytial virus (RSV) for adults ≥ 60 years old, the Advisory Committee on Immunization Practices (ACIP) (a committee of the Centers for Disease Control and Prevention [CDC]) recently recommended using shared decision-making to decide whether to vaccinate.[9] In May of 2023, two vaccines for adults aged 60 and older were approved for use to mitigate the morbidity and mortality associated with RSV in this age group. ACIP based its guidance on evidence of effectiveness in decreasing RSV-associated lower respiratory tract disease. There was insufficient data to assess efficacy of reducing hospitalization, need for respiratory support or death from RSV. Efficacy data were available for a two-year period. The ACIP recommendation is for a one-time dose. Of note, cost-effectiveness was not taken into consideration for this recommendation. Immunizing against RSV is likely most beneficial for groups that are at highest risk of severe disease. These include patients with frailty, advanced age, significant comorbidities (e.g., COPD, heart failure, DM, CKD, cardiovascular or cerebrovascular disease) or suppressed immune systems, as well as those living in group settings (e.g., long-term care facilities). For otherwise healthy community-dwelling adults, from a health systems perspective, at the current cost of roughly $300 USD per injection, the cost-benefit is not clear.

Opioid analgesics have no role in management of pain in typical musculoskeletal-related acute low back pain and neck pain

A multi-center triple-blinded randomized placebo-controlled trial of 347 adult patients presenting with 12 weeks or less of low back and/or neck pain looked at pain severity over time, and at adverse events.[10] Patients were randomized to receive guideline-recommended care plus opioids or guideline-recommended care plus placebo. Most patients (97%) were recruited from primary care office visits, with the remainder recruited from an emergency room visit. For those in the opioid group, a twice-daily combination of oxycodone/naloxone was prescribed according to protocol and titrated based on regular pain score assessment. Opioids were tapered and stopped when pain score decreased to less than 2 on a 10-point scale or at six weeks of treatment, whichever was sooner. At six weeks, the pain scores did not differ significantly between the two groups (2.78 [SE 0.20]) in the opioid group versus 2.25 (0.19) in the placebo group; adjusted mean difference 0.53, 95% CI −0.00 to 1.07, p=0.051). The rates of reported adverse events was similar between the two groups, although unsurprisingly, the known adverse effects of opioids (e.g., constipation, nausea) was more common in the group taking opioids. In addition to the primary outcome of pain score at 6 weeks, secondary outcomes of pain score at 12 weeks, physical functioning, and other proxy measures of health (e.g., work absenteeism, healthcare utilization, etc.) were similar between groups. More people in the opioid group continued to experience pain at 26 weeks, and this was statistically significant at 52 weeks, favoring the placebo. The placebo group scored better on the mental health subscale of the Short Form 36 (SF-36) at weeks 6 and 12.

In summary, this well-designed trial demonstrated no benefit of opioid analgesia for adult patients with acute low back or neck pain and highlights the potential short- and longer-term harms of using this drug class in these conditions.

Trial of direct-acting oral anticoagulant (DOAC) therapy to reduce stroke and CV events in screen-detected atrial fibrillation shows harm

Oral anticoagulation reduces the risk of ischemic stroke among patients with atrial fibrillation (AF). However, the evidence around the outcomes of anticoagulation in subclinical, screen-detected AF is very different. Implantable loop recorders (ILRs) are increasingly being placed to screen for AF. These devices have a cost of approximately $15,000 per patient and patients receive an additional monthly charge for rhythm monitoring. Clinical trial evidence suggests that screening with ILRs among patients with an increased risks of AF and stroke compared to usual care results in three-fold higher AF detection and subsequent anticoagulant use, but no significant reduction in stroke or overall mortality.[11] These devices are also being placed frequently after a diagnosis of stroke of undetermined etiology, again without strong evidence of clinical benefit using this approach. The 2021 American Heart Association / American Stroke Association clinical practice guideline for secondary prevention of ischemic stroke gives a Class 2a recommendation for long-term rhythm monitoring to detect intermittent AF among patients with cryptogenic stroke. This is a moderate recommendation in which benefits are considered to outweigh risks.[12] However, this guideline recommendation is based on three clinical trials that looked solely at AF detection as the primary endpoint, and not based on improved clinical outcomes including reduction in recurrent stroke.[13,14,15]

Added to this body of literature is a new study which randomized 2,536 patients with subclinical, screen-detected AF to receive either edoxaban or placebo.[16] The mean age of the patients was 78 years. The median duration of the AF was 2.8 hours, and atrial rates were generally greater than 200 beats per minute. The median number of episodes was 2.8 in each patient group. The median CHA_2DS_2 -VASc score was 4. The primary efficacy outcome was a composite of cardiovascular death, stroke or systemic embolism, and the safety outcome was a composite of death from any cause or major bleeding. The trial was stopped at a median follow-up of 21 months, owing to safety concerns and the results of an assessment of futility for the efficacy of edoxaban. There was no significant difference in the primary efficacy outcome of 3.2% per patient-year in the edoxaban group and in 4.0% per patient-year in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.60 to 1.08; P=0.15). In terms of harm, a safety outcome event occurred in 5.9% per patient-year in the edoxaban group and in 4.5% per patient-year in the placebo group (hazard ratio, 1.31; 95% CI, 1.02 to 1.67; P=0.03), a finding that was statistically significant.

The authors concluded that oral anticoagulation with edoxaban in patients with screen-detected AF did not result in a lower incidence cardiovascular death, stroke or systemic embolism compared to no anticoagulation. However, edoxaban led to a higher incidence of a composite of death from any cause or major bleeding.

To add to the above study results, our data science team at Optum Center for Research and Innovation (OCRI) in conjunction with cardiology researchers at UCSF, used a large deidentified patient data base to identify 48,801 patients with stroke of undetermined etiology who were studied with ILRs versus continuous external monitoring (CEM) lasting between 2 and 30 days.[17] Consistent with the above studies, compared to those with CEM, the ILR group had higher odds of a new diagnosis of AF resulting in initiation of anticoagulants (OR 2.27; [95% CI 2.09, 2.48]), as well as a higher risk of hemorrhagic stroke (OR of 1.60 [95% CI 1.34, 1.93]). There was no difference in mortality. Unadjusted direct medical cost of monitoring was substantially higher in the ILR group ($13,975) compared to CEM ($449). Our conclusion was that although ILRs were associated with more new diagnoses of AF and more initiations of oral anticoagulation compared to long-term continuous external monitors after stroke, there was no reduction in mortality. This finding along with an increased risk of hemorrhagic stroke and higher costs raise the possibility of increased harm caused by the use of ILRs for this indication. In the absence of studies proving clinical benefit, a reconsideration of the use of ILRs after ischemic stroke is warranted. This study was accepted for presentation at the American Heart Association scientific meeting in November 2023 and has been submitted for publication at JAMA Neurology.

Shared decision-making is critical when discussing breast cancer screening both in the elderly and those with limited life expectancy

Breast cancer is the 2nd most common cancer in women in the United States.[18] Breast cancer screening with mammography has been endorsed as an effective public health measure to reduce morbidity and mortality by several professional bodies, including the U.S. Preventive Services Taskforce (USPSTF).[19] The age range and frequency of screening varies among the recommendations, and there is some concern that uniform or blanket recommendations may result in unnecessary screening with resultant, needless over-exposure to radiation and potential overdiagnosis of breast cancer. Similar to overdiagnosis of other conditions such as low-risk prostate cancer, overdiagnosis of breast cancer refers to a diagnosis of an indolent cancer that would not have resulted in symptoms or other impact to the patient had it not been detected in the first place through routine screening of asymptomatic patients. Ongoing trials, such as the WISDOM study,[20] are investigating the efficacy of a more personalized approach to breast cancer risk stratification and screening recommendations using family history and genomic data.

A recent retrospective cohort study of over 54,000 women over age 69 examined the frequency of potential overdiagnosis of breast cancer.[21] Primary findings suggest in women aged 70–74 years, 31% of breast cancer is over-diagnosed through screening. For the age group of 75–84 years, this is 47%, and for those 85 and above that number is 54%. These numbers were even higher when analyzing subgroups with lower life expectancies. As this is a retrospective cohort study and not a prospective randomized controlled trial, the investigators performed additional sensitivity analyses with even more conservative assumptions and the data showed a persistent, albeit lower (15%–44%), rate of overdiagnosis in all age groups.

While the exact rate of overdiagnosis is difficult to pinpoint, the data indicates the risk of diagnosing breast cancer that would not have resulted in overt disease or death increases with increasing age and with decreasing life expectancy. Therefore, a shared decision-making approach is critical when discussing breast cancer screening in asymptomatic individuals, particularly those over age 74. The goal is to thoroughly explore the risks and benefits of screening alongside the risk tolerances and patient preferences of the individual patient. In cases where breast cancer screening results in a breast cancer diagnosis, shared decision-making regarding treatment is also paramount. Active treatment of low-grade cancers (such as ductal carcinoma in situ) in people with limited life-expectancy or frailty may not improve cancer outcomes or comport with patient values.

Omitting radiation therapy in early-stage breast cancer

Most early breast cancers are treated with breast-conserving surgery followed by local radiation therapy (XRT). XRT involves 3–6 weeks of treatment, is associated with significant short- and long-term toxicities, and is costly. Therefore, an effort is underway to identify a population of women with early-stage breast cancer in whom XRT can be omitted.

A recent large prospective trial enrolled 500 patients aged 55 or older with T1N0 tumors that were estrogen and progesterone receptor positive, HERS-2 negative and had a low Ki67 index (a marker of cellular proliferation).[22] Patients with lobular cancer, tumor multifocality, an extensive intraductal component or lymphovascular invasion were excluded due to a higher risk of recurrence. All patients were treated with endocrine therapy (an aromatase inhibitor or tamoxifen) and prospectively followed for five years. The cumulative incidence of local recurrence, at five years was 2.3% (95% CI, 1.2 to 4.1) with the upper boundary of the confidence interval less than the prespecified boundary of 5%. Overall, there were 11 recurrences, 7 contralateral cancers, 23 second primary cancers, and 6 deaths that were reported as first events, for a total of 47 overall and 5-year disease-free survival of 89.9%. A total of 13 deaths occurred (of which only one was related to breast cancer), for a five-year overall survival of 97.2%.

The number of recurrences in the ipsilateral breast was similar to that of new breast cancers observed in the contralateral breast, suggesting that these ipsilateral cancers may in fact have been new breast cancers, also supported by the fact that of the ten cases of ipsilateral breast cancer observed, four occurred away from the site of the original breast cancer. The authors concluded that women 55 years of age or older with T1N0 tumors meeting the above criteria, had a very low risk of local recurrence at five years after breast-conserving surgery when treated with endocrine therapy alone. They noted that the prospective and controlled nature of this study supported their conclusion that such patients are candidates for omission of radiotherapy. Current guidelines recommend against the use of XRT in women aged 70 and older with early-stage hormone receptor positive tumors, so these patients can avoid XRT following breast conserving therapy.[23] Based on this current trial, women meeting the trial criteria should participate in a shared decision-making discussion about whether to forgo XRT following breast-conserving surgery.

References

1. Galleri. Patient Overview. Screening for multiple cancers is now possible with Galleri.® https://www.galleri.com/patient/the-galleri-test. Accessed May 17, 2023.
2. Carr DJ, Welch HG. Assessing the Clinical Utility of Liquid Biopsies Across 5 Potential Indications From Therapy Selection to Population Screening: A Review [published online ahead of print, 2023 Aug 28]. *JAMA Intern Med*. 2023;10.1001/jamainternmed.2023.3603. doi:10.1001/jamainternmed.2023.3603
3. Dhruva SS, Smith-Bindman R, Redberg RF. The Need for Randomized Clinical Trials Demonstrating Reduction in All-Cause Mortality With Blood Tests for Cancer Screening [published online ahead of print, 2023 Aug 28]. *JAMA Intern Med*. 2023;10.1001/jamainternmed.2023.3610. doi:10.1001/jamainternmed.2023.3610
4. U.S. Preventive Services Taskforce. Recommendations. Aspirin Use to Prevent Cardiovascular Disease: Preventive Medication. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/aspirin-to-prevent-cardiovascular-disease-preventive-medication. Published April 26, 2022. Accessed April 15, 2023.
5. McNeil JJ, Nelson MR, Woods RL, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1519-1528. doi:10.1056/NEJMoa1803955
6. McQuilten ZK, Thao LTP, Pasricha SR, et al. Effect of Low-Dose Aspirin Versus Placebo on Incidence of Anemia in the Elderly: A Secondary Analysis of the Aspirin in Reducing Events in the Elderly Trial [published correction appears in Ann Intern Med. 2023 Jul 25]. *Ann Intern Med*. 2023;176(7):913-921. doi:10.7326/M23-0675
7. McNeil JJ, Wolfe R, Woods RL, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med*. 2018;379(16):1509-1518. doi:10.1056/NEJMoa1805819
8. Cloud GC, Williamson JD, Thao LTP, et al. Low-Dose Aspirin and the Risk of Stroke and Intracerebral Bleeding in Healthy Older People: Secondary Analysis of a Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(7):e2325803. Published 2023 Jul 3. doi:10.1001/jamanetworkopen.2023.25803
9. Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices-United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(29):793-801. Published 2023 Jul 21. doi:10.15585/mmwr.mm7229a4
10. Jones CMP, Day RO, Koes BW, et al. Opioid analgesia for acute low back pain and neck pain (the OPAL trial): a randomised placebo-controlled trial [published correction appears in Lancet. 2023 Aug 19;402(10402):612]. *Lancet*. 2023;402(10398):304-312. doi:10.1016/S0140-6736(23)00404-X
11. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial [published correction appears in Lancet. 2021 Oct 23;398(10310):1486]. *Lancet*. 2021;398(10310):1507-1516. doi:10.1016/S0140-6736(21)01698-6
12. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association [published correction appears in Stroke. 2021 Jul;52(7):e483-e484]. *Stroke*. 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375
13. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370(26):2478-2486. doi:10.1056/NEJMoa1313600
14. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376
15. Wachter R, Gröschel K, Gelbrich G, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRANDOMISED): an open-label randomised controlled trial [published correction appears in Lancet Neurol. 2017 Apr;16(4):261]. *Lancet Neurol*. 2017;16(4):282-290. doi:10.1016/S1474-4422(17)30002-9
16. Kirchhof P, Toennis T, Goette A, et al. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes [published online ahead of print, 2023 Aug 25]. *N Engl J Med*. 2023;10.1056/NEJMoa2303062. doi:10.1056/NEJMoa2303062
17. Druva S, Redberg R, Murillo J, and Cohen K. Mortality, Safety, Utilization and Cost Associated with Implantable Loop Recorders vs External Monitors After Ischemic or Cryptogenic Stroke, *JAMA Neurology*, submitted.
18. Centers for Disease Control and Prevention (CDC). Cancer. Breast Cancer. Breast Cancer Statistics. https://www.cdc.gov/cancer/breast/statistics/index.htm. Last reviewed June 8, 2023. Accessed August 9, 2023.
19. U.S. Preventive Services Taskforce. Recommendations. Breast Cancer: Screening. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-screening. Published January 11, 2016. Accessed August 9, 2023.
20. Wisdom Study. https://www.thewisdomstudy.org/. Accessed August 9, 2023.
21. Richman IB, Long JB, Soulos PR, Wang SY, Gross CP. Estimating Breast Cancer Overdiagnosis After Screening Mammography Among Older Women in the United States [published online ahead of print, 2023 Aug 8]. *Ann Intern Med*. 2023;10.7326/M23-0133. doi:10.7326/M23-0133
22. Whelan TJ, Smith S, Parpia S, et al. Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. *N Engl J Med*. 2023;389(7):612-619. doi:10.1056/NEJMoa2302344
23. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial [published correction appears in Lancet Oncol. 2015 Mar;16(3):e105]. *Lancet Oncol*. 2015;16(3):266-273. doi:10.1016/S1470-2045(14)71221-5

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